Set	Items	Description
S1	1	MULTIDRUG(W)RESISTANCE(W)POLYPEPTIDE
S2	45183	P(W)GLYCOPROTEIN
S3	45184	S1 OR S2
S4	2792530	TRANSFORM?
S5	1429352	CARCINOMA
S6	289280	ADENOCARCINOMA
S7	285818	SARCOMA
S8	818785	LEUKEMIA
S9	416920	LYMPHOMA
S10	11467	LYMPHOSARCOMA
S11	81765	LEUKAEMIA
S12	141	AU="SHYJAN A" OR AU="SHYJAN A." OR AU="SHYJAN ANDREW" OR AU="SHYJAN ANDREW W" OR AU="SHYJAN A.W." OR AU="SHYJAN A W"
S13	4	S12 AND S2
S14	1923	S2 AND S4
S15	2860090	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
S16	72329	MULTIDRUG (S)RESISTAN?
S17	1261	S14 AND S16
S18	722	S17 AND S15
S19	387	S18 NOT PY>1997
S20	323	RD (unique items)
S21	17561	S2/TI
S22	25	S20 AND S21
S23	20	S12 AND S16
S24	16	S23 NOT S13
S25	14	RD (unique items)
S26	0	S25 NOT PY>1997
S27	18465	CYTOTOXIN
S28	40063	MCF(W)7
S29	3	S20 AND S27
S30	3	S29 NOT PY>1997
S31	146	S16 AND S27
S32	73	S31 NOT PY>1997
S33	1980	S16 AND S28
S34	42	RD S32 (unique items)
S35	1980	S28 AND S16
S36	1090	S2 AND S35
S37	288	S21 AND S36
S38	204	S37 NOT PY>1997
S39	75	RD (unique items)

?

22/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08914824 96419341 PMID: 8822114
Proliferative activity in breast carcinoma **evaluated by BrdU and PCNA. Correlation with expression of p53, c-erbB-2, estrogen receptor and** P-glycoprotein.
Moriki T; Takahashi T; Tanioka F; Yamane T; Hara H
Department of Clinical Laboratory Medicine and Pathology, Kochi Medical School, Japan.
Pathology, research and practice (GERMANY) Nov 1995, 191 (11) p1122-32, ISSN 0344-0338 Journal Code: PBZ
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The proliferative activity in 35 cases of breast **carcinoma** was evaluated by bromodeoxyuridine (BrdU) and proliferating cell nuclear antigen (PCNA) and was compared with benign breast lesion. Overexpression of p53 and c-erbB-2 oncoprotein, presence of estrogen receptor (ER) and cellular localization of **multidrug resistance** gene product **P-glycoprotein** (P-gp) were immunohistochemically examined to investigate the relation with the proliferative activity and clinicopathologic characteristics. The mean BrdU labeling index (LI) was 12.6% and PCNA labeling rate (LR) was 33.5% in breast carcinomas, and good correlation was found between them. The proliferative activity of breast carcinomas was significantly higher than that of benign lesions. The BrdU LI correlated positively with tumor size, histologic grade, TNM stage and p53 immunoreactivity, and negatively with the presence of ER. PCNA LR correlated with histologic grade and expression of p53. p53 protein was demonstrated in 43% of the breast carcinomas and correlated with proliferative activity. The extent of p53 immunoreactivity on **carcinoma** cells was also related to BrdU LI. c-erbB-2 oncoprotein was demonstrated in 51% of the breast carcinomas and correlated with histologic grade. ER was found in 34% of the breast carcinomas and correlated negatively with histologic grade, lymph node metastasis and TNM stage. P-gp was observed in 49% of the breast carcinomas and no correlation was found with clinicopathologic characteristics. None of the benign lesions expressed p53 protein, c-erbB-2 oncoprotein and P-gp. BrdU is a reliable standard and a more useful tool for the evaluation of proliferative activity of breast tumors. High proliferative activity, overexpression of p53 protein and the absence of ER are considered as a high grade malignancy of breast **carcinoma** . Expression of c-erbB-2 oncoprotein and P-gp may be related to malignant **transformation** of breast tumors.

22/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08415047 94331307 PMID: 7914421
Reversion of multidrug resistance **in the** P- glycoprotein-**positive human pancreatic cell line (EPP85-181RDB) by introduction of a hammerhead ribozyme.**
Holm PS; Scanlon KJ; Dietel M
Institute of Pathology, Kiel, Germany.
British journal of cancer (SCOTLAND) Aug 1994, 70 (2) p239-43, ISSN 0007-0920 Journal Code: AV4
Contract/Grant No.: CA 50618, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
A major problem in cytostatic treatment of many tumours is the development of **multidrug resistance** (MDR4). This is most often

accompanied by the overexpression of a membrane transport protein, **P - glycoprotein** , and its encoding mRNA. In order to reverse the **resistant** phenotype in cell cultures, we constructed a specific hammerhead ribozyme possessing catalytic activity that cleaves the 3'-end of the GUC sequence in codon 880 of the mdr1 mRNA. We demonstrated that the constructed ribozyme is able to cleave a reduced substrate mdr1 mRNA at the GUC position under physiological conditions in a cell-free system. A DNA sequence encoding the ribozyme gene was then incorporated into a mammalian expression vector (pH beta APr-1 neo) and transfected into the human pancreatic **carcinoma** cell line EPP85-181RDB, which is **resistant** to daunorubicin and expresses the MDR phenotype. The expressed ribozyme decreased the level of mdr1 mRNA expression, inhibited the formation of **P - glycoprotein** and reduced the cell's **resistance** to daunorubicin dramatically; this means that the **resistant** cells were 1,600-fold more **resistant** than the parental cell line (EPP85-181P), whereas those cell clones that showed ribozyme expression were only 5.3-fold more **resistant** than the parental cell line.

22/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08243606 94223909 PMID: 7909572
Clinical relevance of P- glycoprotein **expression in haematological malignancies.**
Nooter K; Sonneveld P
Department of Medical Oncology, Rotterdam Cancer Institute, The Netherlands.
Leukemia research (ENGLAND) Apr 1994, 18 (4) p233-43, ISSN 0145-2126 Journal Code: K9M
Languages: ENGLISH
Document type: Journal Article; Review; Review, Academic
Record type: Completed
Although, generally speaking, haematological malignancies are chemotherapy-responsive tumours and high remission induction rates are obtained, disease-related death is the rule rather than the exception. The appearance of cell populations, **resistant** to **multidrug** -based chemotherapy, constitutes the major problem to achieve cures in these patients. Advances in cell biology have partly contributed to the elucidation of different **multidrug resistance** (MDR) mechanisms, which enable cells to survive the cytotoxic effects of multiple chemotherapeutic agents. Of these **resistance** mechanisms, the one that is referred to as classical MDR is the most extensively studied, both in the laboratory as well as in patients, and here we will focus on its clinical relevance in haematological malignancies. The classical MDR phenotype is caused by enhanced cellular drug efflux due to increased activity of a membrane-bound glycoprotein (**P - glycoprotein**) drug pump, that can pump out anthracyclines, anthracenediones, vinca alkaloids and epipodophyllotoxins, thereby actively lowering the intracellular drug concentrations to sublethal levels. As soon as molecular probes for the detection of MDR cells became available, clinical studies were initiated to answer three main questions. Do human tumor cells express **P -glycoprotein** ? If so, is the expression indicative of a bad prognosis, c.q. **resistant** disease? And last but not least, can we interfere with the **P -glycoprotein** drug pump in the patient? Clinical data indicate that classical MDR may be involved in the development of drug **resistance** , especially in some haematological malignancies, such as acute myelocytic **leukaemia** (AML), non-Hodgkin's lymphomas (NHL), and multiple myelomas (MM). In almost all types of haematological malignancies, either untreated or treated, elevated **P - glycoprotein** levels have been reported, ranging from low to high. However, the acquisition of clinical MDR associated with **P -glycoprotein** expression occurs only in those diseases (for example, AML and MM) that are heavily treated with MDR-related drugs, probably by selection of

pre-existing **P - glycoprotein** -expressing malignant cells. Since **P - glycoprotein** is found to be expressed on the membrane of normal haemopoietic progenitor cells as well, it seems likely that **P - glycoprotein** -positive haematological tumours develop by malignant **transformation** of **P - glycoprotein** -expressing normal haemopoietic counterparts. Especially for AML, convincing data have been reported in the literature to show that **P -glycoprotein** expression at diagnosis is a bad prognostic factor that predicts refractoriness. Using in vitro model systems for classical MDR, a large number of agents have been identified that can circumvent **P - glycoprotein** -mediated drug **resistance** , the so-called **resistance** modifying agents (RMA).(ABSTRACT TRUNCATED AT 400 WORDS)

22/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08008275 93309197 PMID: 8100604
High expression of the multidrug resistance P- glycoprotein **in high-risk myelodysplasia is associated with immature phenotype.**
Sonneveld P; van Dongen JJ; Hagemeijer A; van Lom K; Nooter K; Schoester M; Adriaansen HJ; Tsuruo T; de Leeuw K
Department of Hematology, University Hospital Rotterdam, The Netherlands.
Leukemia (ENGLAND) Jul 1993, 7 (7) p963-9, ISSN 0887-6924 Journal Code: LEU
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The expression of the **multidrug resistance** (MDR-1) gene product, P-170 glycoprotein (P-170) was investigated in 26 patients with low-risk (n = 9) or high-risk (n = 17) myelodysplastic syndrome (MDS), using a panel of monoclonal antibodies to P-170 (C219, JSB1, C494, MRK16) and quantitative analysis of MDR-1 mRNA. P-170 membrane staining was demonstrated in bone marrow blast cells of 14/17 HR-MDS and in 2/9 LR-MDS patients ($p < 0.01$). P-170 expression was associated with the presence of blast cells characterized by an immature or early myeloid phenotype as defined by CD34 expression ($p = 0.034$), CD13 or CD33 expression ($p = 0.0006$), or CD13/33 plus terminal deoxynucleotidyl transferase (TdT) double expression ($p = 0.04$). With double fluorescence analysis, P-170 expression was observed in a subset of CD34+ cells, but not in CD34- cells. P-170 expression was present in 13/15 (86%) patient samples with an abnormal karyotype as compared with 3/10 samples (30%) with a normal karyotype ($p < 0.05$). Nine of these 15 patients had a loss or a deletion of chromosome 7. Thirteen out of 16 (81%) MDR-1 positive patients developed acute **leukemia** versus two of ten (20%) MDR-1 negative patients ($p = 0.025$). It is concluded that MDR-1 expression in MDS is present in cells with an immature phenotype and is frequently observed in patients who have an abnormal karyotype and a high risk of leukemic **transformation** .

22/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06929774 93007984 PMID: 1356622
Decreased P - glycoprotein expression in multidrug-sensitive and - resistant human myeloma cells induced by the cytokine leukoregulin.
Evans CH; Baker PD
Tumor Biology Section, National Cancer Institute, Bethesda, Maryland 20892.
Cancer research (UNITED STATES) Nov 1 1992, 52 (21) p5893-9, ISSN 0008-5472 Journal Code: CNF
Languages: ENGLISH
Document type: Journal Article

Record type: Completed
Modulation of the expression of **P -glycoprotein** , a plasma membrane protein associated with **multidrug resistance** , was examined in drug-sensitive and drug-**resistant** tumor cells treated with leukoregulin, a M(r) 50,000 cytokine from human lymphocytes that rapidly permeabilizes the plasma membrane of many tumor cells facilitating the uptake of doxorubicin and other tumor-inhibitory antibiotics. **P -glycoprotein** expression was measured flow cytometrically by the binding of C219 or MRK16 monoclonal antibody to **multidrug** -sensitive human K562 erythroleukemia and 8226/S myeloma cells, compared to **multidrug** - **resistant** 8226/DOX40 myeloma cells. Cells were treated for up to 2 h with up to 80 units of leukoregulin/ml or one of a variety of unrelated cytokines including interleukin 1 alpha (IL-1 alpha), IL-1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, colony-stimulating factor, macrophage colony-stimulating factor, granulocyte macrophage colony-stimulating factor, tumor necrosis factor alpha, gamma-interferon, alpha-interferon, epidermal growth factor, platelet-derived growth factor AA, platelet-derived growth factor BB, insulin-like growth factor I, insulin-like growth factor II, fibroblast growth factor, or **transforming** growth factor beta. Leukoregulin caused a concentration-dependent decrease in **P -glycoprotein** expression; however, **P -glycoprotein** expression was unaffected by the other cytokines (< 12% decrease in expression). Leukoregulin-induced membrane permeabilization, determined flow cytometrically by intracellular fluorescein efflux, and decreased **P -glycoprotein** expression occurred simultaneously within 15 min in drug-sensitive and -**resistant** cells. Enhanced doxorubicin uptake, measured flow cytometrically by doxorubicin influx, was also present within 15 min. Leukoregulin enhancement of doxorubicin uptake and increased membrane permeability varied directly with the decrease in **P -glycoprotein** expression. Leukoregulin in combination with doxorubicin enhanced the inhibition of cell proliferation in 8226/DOX40 **multidrug -resistant** cells over expressing **P -glycoprotein** . In contrast, combined treatment of HL-60/MX2 **multidrug - resistant** human promyelocytic **leukemia** cells that do not overexpress **P -glycoprotein** in association with their **multidrug resistance** resulted in no greater growth inhibition than observed with HL-60/MX2 cells treated with doxorubicin alone. This is the first demonstration that a naturally occurring macromolecule with anticancer activities can modulate the expression of **P - glycoprotein** concomitant with enhanced drug uptake and inhibition of cell proliferation.

22/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06847195 91304055 PMID: 1677057
P - glycoprotein **expression and in vitro reversion of doxorubicin resistance by verapamil in clinical specimens from acute** leukaemia **and myeloma.**
Solary E; Bidan JM; Calvo F; Chauffert B; Caillot D; Mugneret F; Gauville C; Tsuruo T; Carli PM; Guy H
Service d'Hematologie Clinique, CHU Le Bocage, Dijon, France.
Leukemia (ENGLAND) Jul 1991, 5 (7) p592-7, ISSN 0887-6924
Journal Code: LEU
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The expression of the **P -glycoprotein** which is associated with the development of **multidrug resistance** in various cell lines was investigated in 87 fresh acute **leukaemia** and multiple myeloma samples using the specific mouse monoclonal antibody MRK16 in an indirect immunofluorescence assay. Considering a 10% positive cell cut-off value, a heterogeneous expression of **P -glycoprotein** was observed in 5/22 (22.7%) de novo acute leukaemias, 7/22 (31.8%) relapse or secondary acute

leukaemias, 14/27 (51.8%) acute **transformation** of myeloproliferative or myelodysplastic syndromes and 5/16 (31.2%) multiple myelomas. This expression was not associated with specific cytogenetic abnormalities, especially alterations of chromosome 7q. Verapamil, a calcium channel blocker, has been demonstrated to circumvent the **multidrug resistance** in cell lines, possibly by interfering with **P -glycoprotein** function. Using the microculture tetrazolium assay, verapamil was demonstrated to increase the sensitivity of fresh leukaemic or myeloma cells to doxorubicin in 19/43 (43.1%) samples. The doxorubicin IC50 level and the capacity of verapamil to increase the sensitivity of blast cells to doxorubicin in vitro did not correlate with the expression of **P -glycoprotein** . We conclude that high non-cytotoxic concentrations of verapamil were able to increase the in vitro doxorubicin sensitivity of fresh acute **leukaemia** and myeloma cells without detectable expression of the **P -glycoprotein** .

22/3,AB/9 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10064058 BIOSIS NO.: 199598518976
Expression of CD34 and P- glycoprotein**: Prognostic significance in primary myelodysplastic syndromes.**
AUTHOR: Runde Volker(a); Germing Ulrich; Aul Carlo
AUTHOR ADDRESS: (a)Dep. Internal Med., Hematology Oncol. Div., Heinrich Heine Univ., Moorenstrasse 5, D-40225 Duess**Germany
JOURNAL: International Journal of Oncology 7 (4):p901-905 1995
ISSN: 1019-6439
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Expression of stem cell phenotype (CD34) and **multidrug resistance** (MDR) on blast cells of 49 untreated patients with primary myelodysplastic syndromes (MDS) was studied by means of the alkaline phosphatase antialkaline phosphatase technique (APAAP). In 29 patients (59%) CD34 and in 19 patients (39%) MDR positivity was found. Both immunocytological markers showed a strong positive correlation (p lt 0.0005) and MDR expression was only detectable in CD34 positive cases. When comparing CD34 and MDR expression with well established prognostic parameters, medullary bone marrow (BM) blast percentage was found to be the sole variable which correlated with expression of both cell surface markers. CD34 and MDR negative patients had a better prognosis although only the difference between CD34 positive and CD34 negative cases reached statistical significance. Regarding the prognostic value of immunocytological results and other clinical and hematological parameters medullary blast cell infiltration remained the strongest predictive variable for survival and AML **transformation** . In 6 patients sequential immunocytological analysis during progression of disease were performed. In contrast to stable CD34 expression a marked increase in MDR expression after AML development could be noted in 2 cases.

1995

22/3,AB/12 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04920066 Genuine Article#: UR843 Number of References: 48
Title: SELECTIVE DRUG EFFLUX IN MULTIDRUG- RESISTANT **IMMUNOBLASTIC B-**LYMPHOMA-**CELLS WITH OVEREXPRESSED** P- GLYCOPROTEIN (Abstract Available)

Author(s): CHAO CCK
Corporate Source: CHANG GUNG MED COLL,DEPT BIOCHEM,TUMOR BIOL LAB/TAYUAN 33332//TAIWAN/
Journal: ENVIRONMENTAL TOXICOLOGY AND PHARMACOLOGY, 1996, V1, N1 (FEB 15), P63-72
ISSN: 1382-6689
Language: ENGLISH Document Type: ARTICLE
Abstract: **Multidrug -resistant** (MDR) sublines of the immunoblastic B **lymphoma** cell line were established by sequentially selecting in increasing concentrations of vincristine or adriamycin. The vincristine- and adriamycin-**resistant** cell lines, HOB1/VCR and HOB1/ADR, respectively, demonstrated **resistance** to a wide spectrum of chemotherapeutic agents including MDR drugs (Vinca alkaloids and anthracycline), antimicrotubule drugs (colchicine), and DNA-damaging agents (cisplatin and mitomycin C). The expression of human mdr1 gene, as analyzed by Western blotting and reverse transcription-polymerase chain reaction (RT-PCR), revealed a 10-15-fold overexpression in both drug-**resistant** cell lines. Drug accumulation analysis demonstrated reduced accumulation of vincristine but not adriamycin in HOB1/VCR and HOB1/ADR cell lines. Inhibition of vincristine **resistance** was observed in both cell lines by verapamil, associated with restoration of drug accumulation, suggesting that acquired **resistance** in these cells is mainly due to **P -glycoprotein** . The drug accumulation was also examined in two series of previously characterized adriamycin-selected MDR colon **adenocarcinoma** cells and vincristin-selected non-MDR lung cancer cells. These studies demonstrated that immunoblastic B **lymphoma** cells selected for vincristine or adriamycin **resistance** preferentially develop **P -glycoprotein** -mediated vincristine efflux which plays a pivotal role in vincristine **resistance** . Tn contrast, these cells did not elevate adriamycin efflux, suggesting an additional mechanism responsible for adriamycin **resistance** .

22/3,AB/13 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04361851 Genuine Article#: RY141 Number of References: 35
Title: INFLUENCE OF EXOGENOUS RAS AND P53 ON P- GLYCOPROTEIN **FUNCTION IN IMMORTALIZED RODENT FIBROBLASTS** (Abstract Available)
Author(s): KOPNIN BP; STROMSKAYA TP; KONDRATOV RV; OSSOVSKAYA VS; PUGACHEVA EN; RYBALKINA EY; KHOKHLOVA OA; CHUMAKOV PM
Corporate Source: CANC RES CTR,INST CANCEROGENESIS,DEPT CYTOGENET/MOSCOW 115478//RUSSIA/; RUSSIAN ACAD SCI,VA ENGELHARDT MOLEC BIOL INST/MOSCOW 117984//RUSSIA/
Journal: ONCOLOGY RESEARCH, 1995, V7, N6, P299-306
ISSN: 0965-0407
Language: ENGLISH Document Type: ARTICLE
Abstract: The ability of ras oncogenes and mutant p53 to activate reporter gene expression from human and rodent mdr1 gene promoters was described, although functional significance of this finding was unclear. We analyzed the influence of various forms of recombinant human ras and p53 on the mdr1 gene expression and **P -glycoprotein** (Pgp) function in rodent immortalized fibroblasts. The ras genes, in addition to activation of exogenous human mdr1 gene promoter, caused an increase in (i) expression of endogenous mdrl mRNA, (ii) Pgp activity as determined by flow cytometry analysis of Rhodamine 123 exclusion, and (iii) **resistance** of cells to the cytotoxic action of colchicine and some other drugs. To elucidate whether the same signalling pathway is responsible for **multidrug resistance** induced by various oncogenes and protein kinase C (PKC), we tested the effects of v-mos and the PKC agonist 12-O-tetradecanoylphorbol-13-acetate. Similarly to

cells **transformed** by ras, a Rat1 subline **transformed** by the v-mos oncogene was characterized by decreased drug sensitivity. On the contrary, Rat1 cells treated with the protein kinase C agonist 12-O-tetradecanoylphorbol-13-acetate showed neither increased mdr1 mRNA expression nor stimulation of Pgp function. Introduction by retrovirus-mediated gene transfer of wild-type p53 into Rat1 cells or into murine p53-deficient 10(1) and 10(3) cells did not change the Pgp function significantly, whereas in Rat1 cells **transformed** by activated N-ras or v-mos, expression of wild-type p53 caused partial reversion of oncogene-induced drug **resistance** . In agreement with previously published results, we observed that in a transient transfection assay a majority of p53 mutants stimulated reporter gene expression from an exogenous mdr1 promoter in murine cells. However, in Rat1, 10(1) and 10(3) cell sublines, which permanently express various p53s as a result of retroviral transfer, we found neither increase in mdr1 mRNA expression and activation of the mdr1 gene promoter, nor increased drug **resistance** . Moreover, in ras- and mos-**transformed** Rat1 cells some p53 mutants (His-273, Trp-248), similarly to wild-type p53, caused a slight decrease in **resistance** to colchicine. On the other hand, Tyr-141 p53 decreased drug **resistance** of Rat1 and Rat/mos but not Rat/ras cells. Weak effects of physiological concentrations of p53 proteins on mdr1 gene expression and Pgp function as well as differential influence of various p53 mutants on **multidrug resistance** in various cell contexts allow us to suppose that p53 may influence mdr1 gene expression through other transcription factors, rather than by its direct interaction with the mdr1 gene.

22/3,AB/15 (Item 5 from file: 34)

03271684 Genuine Article#: NR463 Number of References: 24

Title: SURAMIN INHIBITS THE GROWTH OF HUMAN BREAST-CANCER CELL-LINES - STUDIES ON PARENTAL LINES AND CORRESPONDING SUBLINES WITH ACQUIRED DOXORUBICIN RESISTANCE WITH AND WITHOUT EXPRESSION OF P- GLYCOPROTEIN (Abstract Available)

Author(s): LINDMAN H; TAUBE A; BERGH JCS
Corporate Source: UNIV UPPSALA,AKAD SJUKHUSET,DEPT ONCOL/S-75185 UPPSALA//SWEDEN/; UNIV UPPSALA,AKAD SJUKHUSET,DEPT ONCOL/S-75185 UPPSALA//SWEDEN/; UPPSALA UNIV,DEPT STAT/UPPSALA//SWEDEN/

Journal: ANTICANCER RESEARCH, 1994, V14, N2A (MAR-APR), P363-366
ISSN: 0250-7005
Language: ENGLISH Document Type: ARTICLE

Abstract: Suramin at 100 to 800 mu g/ml caused a dose dependent growth inhibition in three (Zr-75-1, BT 549 and HS-578T) parental human breast cancel cell lines and their corresponding sublines with acquired doxorubicin (dox) and multi-drug **resistance** . The effect was significantly more marked after 7 days suramin exposure compared with 3 days. The oestrogen and progesterone receptor rich cell line Zr-75-1 was more responsive to suramin compared with the other two lines. The sublines Zr-75-1-dox and HS-578T-dox with art increased expression of the permeability glycoprotein (P-gp) demonstrated a significantly decreased cell survival compared with corresponding parental cell lines at 3 and 7 days exposure of suramin, respectively. The subline BT 549-dox with **multidrug resistance** without P-gp expression had a significantly impaired response after 3 days suramin compared with the parental line. These results indicate that suramin may be a potential therapeutic agent for the breast cancer patients with P-gp expression and multi-drug **resistance** .

22/3,AB/16 (Item 6 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

02902011 Genuine Article#: MM981 Number of References: 59
Title: FUNCTIONAL EXPRESSION OF P- GLYCOPROTEIN IN SACCHAROMYCES-CEREVISIAE CONFERS CELLULAR-RESISTANCE TO THE IMMUNOSUPPRESSIVE AND ANTIFUNGAL AGENT FK520 (Abstract Available)
Author(s): RAYMOND M; RUETZ S; THOMAS DY; GROS P
Corporate Source: MCGILL UNIV,DEPT BIOCHEM,3655 DRUMMOND/MONTREALH3G 1Y6/QUEBEC/CANADA/; MCGILL UNIV,DEPT BIOCHEM,3655 DRUMMOND/MONTREALH3G 1Y6/QUEBEC/CANADA/; NATL RES COUNCIL CANADA,BIOTECHNOL RES INST/MONTREAL H4P 2R2/PQ/CANADA/; MCGILL UNIV,DEPT BIOL/MONTREAL H3A 1B1/QUEBEC/CANADA/
Journal: MOLECULAR AND CELLULAR BIOLOGY, 1994, V14, N1 (JAN), P277-286
ISSN: 0270-7306
Language: ENGLISH Document Type: ARTICLE
Abstract: We have recently reported that expression in yeast cells of **P - glycoprotein** (P-gp) encoded by the mouse **multidrug resistance** mdr3 gene (Mdr3) can complement a null ste6 mutation (M. Raymond, P. Gros, M. Whiteway, and D. Y. Thomas, Science 256:232-234, 1992). Here we show that Mdr3 behaves as a fully functional drug transporter in this heterologous expression system. Photolabelling experiments indicate that Mdr3 synthesized in yeast cells binds the drug analog [I-125]iodoaryl azidoprazosin, this binding being competed for by vinblastine and tetraphenylphosphonium bromide, two known **multidrug resistance** drugs. Spheroplasts expressing wild-type Mdr3 (Ser-939) exhibit an ATP-dependent and verapamil-sensitive decreased accumulation of [H-3]vinblastine as compared with spheroplasts expressing a mutant form of Mdr3 with impaired transport activity (Phe-939). Expression of Mdr3 in yeast cells can confer **resistance** to growth inhibition by the antifungal and immunosuppressive agent FK520, suggesting that this compound is a substrate for P-gp in yeast cells. Replacement of Ser-939 in Mdr3 by a series of amino acid substitutions is shown to modulate both the level of cellular **resistance** to FK520 and the mating efficiency of yeast mdr3 **transformants** . The effects of these mutations on the function of Mdr3 in yeast cells are similar to those observed in mammalian cells with respect to drug **resistance** and transport, indicating that transport of a-factor and FK520 in yeast cells is mechanistically similar to drug transport in mammalian cells. The ability of P-gp to confer cellular **resistance** to FK520 in yeast cells establishes a dominant phenotype that can be assayed for the positive selection of intragenic revertants of P-gp inactive mutants, an important tool for the structure-function analysis of mammalian P-gp in yeast cells.

22/3,AB/18 (Item 8 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

00991837 Genuine Article#: FM005 Number of References: 41
Title: EXPRESSION OF THE MULTIDRUG RESISTANCE GENE-PRODUCT (P-GLYCOPROTEIN) IN MYELODYSPLASIA IS ASSOCIATED WITH A STEM-CELL PHENOTYPE (Abstract Available)
Author(s): LIST AF; SPIER CM; CLINE A; DOLL DC; GAREWAL H; MORGAN R; SANDBERG AA
Corporate Source: DEPT VET AFFAIRS MED CTR,SECT HEMATOL ONCOL,111-D,3501 S 6TH AVE/TUCSON//AZ/85723; UNIV ARIZONA,ARIZONA HLTH SCI CTR/TUCSON//AZ/85724; SW BIOMED RES INST,CTR CANC/SCOTTSDALE//AZ/00000
Journal: BRITISH JOURNAL OF HAEMATOLOGY, 1991, V78, N1, P28-34
Language: ENGLISH Document Type: ARTICLE
Abstract: Previous studies have indicated relative **resistance** to chemotherapy in the myelodysplastic syndromes (MDS) and associated

acute **leukaemia** . To determine if **multidrug resistance** may contribute to chemoresistance in these disorders, we studied bone marrow specimens for **P -glycoprotein** expression (P-GP) by immunocytochemical staining with monoclonal antibodies reactive with cytoplasmic (C219) or surface epitopes (MRK16) of P-GP. Forty-five case specimens from 43 patients were studied, including 32 cases of primary MDS, seven cases of acute myeloid **leukaemia** (AML) following MDS, and six therapy-related haematological disorders. Cytogenetic analysis was available on 36 specimens. Two staining patterns were detected: (1) cytoplasm and plasma membrane, and (2) staining restricted primarily to the nuclear-cytoplasmic junction. P-GP was detected in seven (22%) cases of primary MDS, four (57%) cases of AML evolving from MDS, and five (83%) cases of therapy-related haematological disorders. Expression of P-GP was restricted to blasts and leukaemic monocytes, and was otherwise absent from terminally differentiated blood cells. Analysis of the relation between P-GP expression and reactivity with the human progenitor cell antigen CD34, revealed a highly significant association (P = 0.001). P-GP reactivity was distributed equally among normal and abnormal karyotypes and did not correlate with specific cytogenetic abnormalities. These findings indicate that **multidrug resistance** in MDS and karyotypically-related haematological disorders is closely linked to a stem cell phenotype and may contribute to chemoresistance in these disorders.

22/3,AB/21 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

05662654 EMBASE No: 1994073854
Characteristics of P388/VMDRC.04, a simple, sensitive model for studying P- glycoprotein **antagonists**
Yang J.-M.; Goldenberg S.; Gottesman M.M.; Hait W.N.
Cancer Institute of New Jersey, CABM Building, 679 Hoes Lane,Piscataway, NJ 08854-5638 United States
Cancer Research (CANCER RES.) (United States) 1994, 54/3 (730-737)
CODEN: CNREA ISSN: 0008-5472
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Cross-resistance to chemotherapeutic drugs is a significant problem in the treatment of patients with cancer. The discovery that this phenomenon is associated with the overexpression of a membrane glycoprotein, **P -glycoprotein** , which acts as a drug efflux pump, has provided a new target for drug development. To develop a model for identifying new compounds which can block the function of **P -glycoprotein** , we infected P388 mouse leukemic cells with a retrovirus containing a cloned human MDR1 complementary DNA. The new cell line, P388/VMDRC.04, incorporated and overexpressed the human gene as evidenced by Southern blots, increased mRNA and protein synthesis, and recognition by the MRK16 monoclonal antibody. P388/VMDRC.04 was cross- resistant to colchicine, vincristine, and doxorubicin, and the degree of resistance correlated with a reduction in cellular drug accumulation. Unlike many cell lines selected for resistance by growth in increasing concentrations of drug for prolonged periods of time, these cells did not show alternative mechanisms of resistance such as increased synthesis of glutathione or alterations in topoisomerase II. In addition, the sensitivity of P388/VMDRC.04 cells was completely restored by cyclosporin A and trans- flupenthixol. P388/VMDRC.04 cells were subcloned and 10 clones were picked for in vivo evaluation. One subclone grew similarly to parental cells in female BALB/c x DBA/2 Finf 1 mice and showed no responsiveness to therapeutic doses of vincristine or etoposide. The combination of vincristine with cyclosporin A significantly increased the

survival of mice inoculated with P388/VMDRC.04 cells. The availability of a cell line that displays the MDR phenotype, overexpresses human **P -glycoprotein** , but does not contain alterations in at least two well-defined alternative mechanisms of resistance, and that can be grown in simple animal models should facilitate the development of new agents active against this form of chemotherapeutic drug resistance.

22/3,AB/23 (Item 1 from file: 434)
DIALOG(R)File 434:SciSearch(R) Cited Ref Sci

07861811 Genuine Article#: F8526 Number of References: 24
Title: EXPRESSION OF HAMSTER P- GLYCOPROTEIN **AND** MULTIDRUG RESISTANCE **IN DNA-MEDIATED** TRANSFORMANTS **OF MOUSE LTA CELLS**
Author(s): DEUCHARS KL; DU RP; NAIK M; EVERNDENPORELLE D; KARTNER N; VANDERBLIEK AM; LING V
Corporate Source: UNIV TORONTO,PRINCESS MARGARET HOSP,ONTARIO CANC INST/TORONTO M4X 1K9/ONTARIO/CANADA/; UNIV TORONTO,DEPT MED BIOPHYS/TORONTO M4X 1K9/ONTARIO/CANADA/; NETHERLANDS CANC INST,DIV MOLEC BIOL/1066 CX AMSTERDAM//NETHERLANDS/
Journal: MOLECULAR AND CELLULAR BIOLOGY, 1987, V7, N2, P718-724
Language: ENGLISH Document Type: ARTICLE

22/3,AB/24 (Item 1 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

02581810
Utility
SCREENING METHOD FOR THE IDENTIFICATION OF BIOENHANCERS THROUGH THE INHIBITION OF **P GLYCOPROTEIN** TRANSPORT IN THE GUT OF A MAMMAL
[Identifying compounds useful for increasing bioavailability of drug in mammal]

PATENT NO.: 5,567,592
ISSUED: October 22, 1996 (19961022)
INVENTOR(s): Benet, Leslie, Belvedere, CA (California), US (United States of America)
Wu, Chi Y., San Francisco, CA (California), US (United States of America)
ASSIGNEE(s): Regents of the University of California, (A U.S. Company or Corporation), Oakland, CA (California), US (United States of America)
[Assignee Code(s): 13234]
APPL. NO.: 8-190,288
FILED: February 02, 1994 (19940202)

This invention was made with Government support under Grant No. GM 26691, awarded by the National Institutes of Health. The Government has certain rights in this invention.

FULL TEXT: 1524 lines

ABSTRACT

A screening method for the identification of bioenhancers that increase the bioavailability of an orally administered pharmaceutical compound through the inhibition of **P -glycoprotein** transport activity in the gut of a mammal is disclosed. These compounds increase the systemic availability of a pharmaceutical compound when administered prior to, or concurrently with,

that compound.
?

34/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09545813 97418091 PMID: 9272128
Modulation and prevention of multidrug resistance **by inhibitors of P-glycoprotein.**
Sikic BI; Fisher GA; Lum BL; Halsey J; Beketic-Oreskovic L; Chen G
Department of Medicine, Stanford University School of Medicine, California, USA.
Cancer chemotherapy and pharmacology (GERMANY) 1997, 40 Suppl pS13-9, ISSN 0344-5704 Journal Code: C9S
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed
Intrinsic and acquired **multidrug resistance** (MDR) in many human cancers may be due to expression of the **multidrug** transporter P-glycoprotein (Pgp), which is encoded by the mdr1 gene. There is substantial evidence that Pgp is expressed both as an acquired mechanism (e.g., in leukemias, lymphomas, myeloma, and breast and ovarian carcinomas) and constitutively (e.g., in colorectal and renal cancers) and that its expression is of prognostic significance in many types of cancer. Clinical trials of MDR modulation are complicated by the presence of multiple-drug-**resistance** mechanisms in human cancers, the pharmacokinetic interactions that result from the inhibition of Pgp in normal tissues, and, until recently, the lack of potent and specific inhibitors of Pgp. A large number of clinical trials of reversal of MDR have been undertaken with drugs that are relatively weak inhibitors and produce limiting toxicities at doses below those necessary to inhibit Pgp significantly. The advent of newer drugs such as the cyclosporin PSC 833 (PSC) provides clinicians with more potent and specific inhibitors for MDR modulation trials. Understanding how modulators of Pgp such as PSC 833 affect the toxicity and pharmacokinetics of cytotoxic agents is fundamental for the design of therapeutic trials of MDR modulation. Our studies of combinations of high-dose cyclosporin (CsA) or PSC 833 with etoposide, doxorubicin, or paclitaxel have produced data regarding the role of Pgp in the clinical pharmacology of these agents. Major pharmacokinetic interactions result from the coadministration of CsA or PSC 833 with MDR-related anticancer agents (e.g., doxorubicin, daunorubicin, etoposide, paclitaxel, and vinblastine). These include increases in the plasma area under the curve and half-life and decreases in the clearance of these cytotoxic drugs, consistent with Pgp modulation at the biliary lumen and renal tubule, blocking excretion of drugs into the bile and urine. The biological and medical implications of our studies include the following. First, Pgp is a major organic cation transporter in tissues responsible for the excretion of xenobiotics (both drugs and toxins) by the biliary tract and proximal tubule of the kidney. Our clinical data are supported by recent studies in mdr-gene-knockout mice. Second, modulation of Pgp in tumors is likely to be accompanied by altered Pgp function in normal tissues, with pharmacokinetic interactions manifesting as inhibition of the disposition of MDR-related cytotoxins (which are transport substrates for Pgp). Third, these pharmacokinetic interactions of Pgp modulation are predictable if one defines the pharmacology of the modulating agent and the combination. The interactions lead to increased toxicities such as myelosuppression unless doses are modified to compensate for the altered disposition of MDR-related cytotoxins. Fourth, in serial studies where patients are their own controls and clinical **resistance** is established, remissions are observed when CsA or PSC 833 is added to therapy, even when doses of the **cytotoxin** are reduced by as much as 3-fold. This reversal of clinical drug **resistance** occurs particularly when the tumor cells express the mdr1 gene. Thus, tumor regression can be obtained without apparent increases in normal tissue toxicities. In parallel with these trials, we have recently demonstrated in the laboratory that PSC 833 decreases the mutation rate for **resistance** to

doxorubicin and suppresses activation of mdr1 and the appearance of MDR mutants. These findings suggest that MDR modulation may delay the emergence of clinical drug **resistance** and support the concept of prevention of drug **resistance** in the earlier stages of disease and the utilization of time to progression as an important endpoint in clinical trials. Pivotal phase III trials to test these concepts with PSC 833 as an MDR modulator are under way or planned for patients with acute myeloid leukemias, multiple myeloma, and ovarian carcinoma.

34/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08997563 96361727 PMID: 8742100
Effect of modulators of the multidrug resistance **pump on the distribution of vinblastine in tissues of the mouse.**
Lyubimov E; Lan LB; Pashinsky I; Stein WD
Biological Chemistry Department, Silberman Institute of Life Sciences, Hebrew University, Jerusalem, Israel.
Anti-cancer drugs (ENGLAND) Jan 1996, 7 (1) p60-9, ISSN 0959-4973 Journal Code: A9F
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Vinblastine at doses ranging from 0.2 to 6 mg/kg body weight was administered i.p. to mice in the absence or presence of the drugs PSC 833, cyclosporin A, mefloquine, quinidine and dipyridamole, all compounds that modulate the **multidrug resistance** pump and thus increase the accumulation of this **cytotoxin** in drug-**resistant** cells in cell culture. In the absence of modulators, vinblastine accumulated in tissues to different extents--lowest in brain, highest in pancreas and intestine. The extent of accumulation was directly proportional to the vinblastine dose in the range 0.2-6 mg/kg body weight. Both at high and low vinblastine doses, all the modulators except quinidine increased the ability of liver, kidney, intestine and lung to accumulate vinblastine by up to 5-fold, and with the further exception of mefloquine, also increased vinblastine levels in pancreas. Only dipyridamole had a marked effect also in brain. Cyclosporin A provided effective increases in the tissue distribution of vinblastine at plasma concentrations similar to those needed to block the **multidrug** pump in the case of cells in cell culture. For mefloquine, plasma concentrations three or four times higher were needed in vivo than were found to be effective in cell culture. The mouse system provides a quick and reliable in vivo method to assay modulators before they are tested in the clinic.

34/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08841576 96203729 PMID: 8616910
Kinetic parameters for reversal of the multidrug pump as measured for drug accumulation and cell killing.
Lan LB; Ayesh S; Lyubimov E; Pashinsky I; Stein WD
Biochemistry Department, Silberman Institute of Life Sciences, Hebrew University, Jerusalem, Israel.
Cancer chemotherapy and pharmacology (GERMANY) 1996, 38 (2) p181-90, ISSN 0344-5704 Journal Code: C9S
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We determined the kinetic parameters that describe the effect of 20 different modulators of the **multidrug resistance** pump on the reversal of **cytotoxin** accumulation in a **resistant** strain of P388 leukemia cells (P388/ADR), and on the reversal of cell killing for these cells. When

measured by a direct comparison of the amplitude of the pertinent protocol (accumulation or cell killing), the Ki for reversal of accumulation was generally some four or five times larger than that for reduction of cytotoxicity. We showed that this was only an apparent discrepancy, since a full theoretical analysis of the two protocols allowed the intrinsic Ki to be obtained for the two procedures and these computed Ki values were then almost identical. We found that for six of the modulators studied (namely, cyclosporin A, quinidine, dipyridamole, propafenone, mefloquine, tamoxifen) the extent of pump reversal should be better than 90% at tolerated plasma levels culled from the literature.

34/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08552511 95329102 PMID: 7605346
Isolation and characterization of a cell line resistant to 5-[3-(2-nitro-1-imidazoyl)-propyl]-phenanthridinium bromide (2-NLP-3), a DNA-intercalating hypoxic cell radiosensitizer and cytotoxin.
Cowan DS; McClelland RA; Rauth AM
Experimental Therapeutics Division, Ontario Cancer Institute, Toronto, Canada.
Biochemical pharmacology (ENGLAND) Jun 29 1995, 50 (1) p61-8, ISSN 0006-2952 Journal Code: 9Z4
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
A DNA-targeted hypoxic cell radiosensitizer and **cytotoxin**, 5-[3-(2-nitro-1-imidazoyl)-propyl]-phenanthridinium bromide (2-NLP-3), has been shown previously to have increased efficacy over untargeted analogues in vitro. To further study the mechanism of action of this compound, a cell line, CHO-1000, derived from Chinese hamster ovary (CHO) AA8-4 cells was isolated. This cell line is capable of continuously growing in a concentration of 2-NLP-3 approximately 10-fold greater than that tolerated by wild-type CHO cells. The **resistance** of CHO-1000 to 2-NLP-3 was compared with that of the P-glycoprotein overexpressing, **multidrug resistant** Chinese hamster cell line CHR-C5 (C5). The **resistance** of CHO-1000 cells to the acute toxic effects of 2-NLP-3 under both hypoxic and aerobic exposure conditions was intermediate to that of the sensitive CHO wild-type cells and the **resistant** C5 cells. A similar pattern was seen for the hypoxic cell radiosensitizing ability of 2-NLP-3. 2-NLP-3 produced significant depletion of glutathione under both hypoxic and aerobic conditions in all three cell lines studied, and the degree of depletion was correlated with drug toxicity. CHO-1000 and C5 cells were significantly more **resistant** to colchicine and doxorubicin compared with wild-type cells. The toxicity pattern of 2-NLP-3 and its comparison phenanthridinium ion, P3, was not the same for CHO-1000 cells compared with C5 cells. Verapamil was an effective agent for reversing the hypoxic **resistance** to 2-NLP-3 in both CHO-1000 and C5 cells, but only a partial reversal of aerobic **resistance** was observed in CHO-1000 cells. These results indicate that the **resistant** phenotype of CHO-1000 is mediated to some degree by P-glycoprotein expression, but that other as yet unidentified factors are also involved.

34/3,AB/8 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11401797 BIOSIS NO.: 199800183129
SDZ PSC 833: A new multidrug resistance **modulator.**
AUTHOR: Covelli Alfredo(a)
AUTHOR ADDRESS: (a)Clin. Res. and Dev., Novartis, Lichstr. 15, CH-4002

Basel**Switzerland
JOURNAL: Tumori 83 (5 SUPPL.):pS21-S24 Sept.-Oct., 1997
ISSN: 0300-8916
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: Italian; Non-English
SUMMARY LANGUAGE: English

ABSTRACT: SDZ PSC 833 is a novel compound able to reverse the **resistance** to chemotherapy of cancer cells with the **multidrug resistance** (MDR) phenotype by inhibiting the 170 kd P-glycoprotein (P-gp). In vitro studies show that SDZ PSC 833 directly interacts with, but is not transported by P-gp, although the exact mechanism of action has not yet been defined. In cells with the MDR phenotype, intracellular concentration of various P-gp-transported anticancer drugs is restored to the same level as in sensitive cells by SDZ PSC 833 concentrations of 0.8 muM to 3.0 muM. In vivo SDZ PSC 833 was highly active in potentiating the antitumour activity of all tested anticancer drugs (ACs) in both sensitive and MDR tumours. Sensitivity of non-MDR tumours was increased by SDZ PSC 833 through pharmacokinetic interactions, that result in enhanced area-under-the-curve (AUC) of P-gp-transported ACs. However, an increased AC bioavailability is not sufficient to explain the therapeutic benefit of SDZ PSC 833 co-treatment in MDR tumour-bearing mice: in these animals, no survival increase could be achieved with the AC alone by simply increasing the **cytotoxin** dosage up to doses that were severely toxic for the non-tumour-bearing mice. In a series of phase I/II studies, the recommended doses of SDZ PSC 833 were established at: 10 mg/kg/day iv as a 24-hour continuous infusion after a 2 mg/kg loading dose as a 2-hour infusion; 20 mg/kg orally divided four times daily in solid tumours or 16 mg/kg orally divided four times daily in multiple myeloma. The dose limiting toxicity of SDZ PSC 833 is ataxia, which appears to be reversible and dose-related. Moreover, a predictable change in pharmacokinetic parameters of concomitantly administered P-gp-transported AC(s) which usually necessitate a 30-60% reduction from the standard dose of the AC in order to maintain the same time-exposure and dose-related toxicity of the cytotoxic drug alone. The results of experiments both in vitro and in vivo suggested that adequate blood levels (ie gtoreq 1.0 muM) of SDZ PSC 833 must be reached before and maintained during the administration of concomitant AC(s), in order to maximally reverse MDR. At the recommended doses, blood concentrations exceeding 1000 ng/mL (1.0 muM) can be achieved after both iv and oral administration. Indeed, SDZ PSC 833 concentrations that fully reverse MDR in vitro are achievable in vivo: plasma samples from patients treated with SDZ PSC 833 restored the sensitivity of MDR human sarcoma cells to paclitaxel, etoposide and doxorubicin. Clinical studies completed so far aimed first to determine the dose of both SDZ PSC 833 and the concomitant AC(s) to be used in ongoing pivotal trials. These studies accrued advanced stage cancer patients, however, tumour responses have been observed in both solid and hematological tumours. The in vitro finding that treatment with SDZ PSC 833 may suppress the activation of the MDR1 gene and prevent the emergence of **resistant** cancer cell clones with the MDR phenotype might support the use of this MDR modulator in earlier stages of disease.

1997

34/3,AB/9 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11119830 BIOSIS NO.: 199799740975
Microfilament depletion and circumvention of multiple drug resistance by sphinxolides.

AUTHOR: Zhang Xinqun; Minale Luigi; Zampella Angela; Smith Charles D(a)
AUTHOR ADDRESS: (a)Dep. Pharmacol., Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, PA 19111**USA
JOURNAL: Cancer Research 57 (17):p3751-3758 1997
ISSN: 0008-5472
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Sphinxolides, a newly described family of cytotoxins from the New Caledonian sponge Neosiphonia superstes, bear structural resemblance to scytophycins. We now demonstrate that the cytotoxicity of sphinxolides is associated with cell cycle arrest in G-2-M and induction of apoptosis. Like scytophycins and cytochalasins, sphinxolides caused rapid loss of microfilaments in cultured cells, without affecting microtubule organization. Microfilament reassembly was very slow after removal of the sphinxolide, consistent with the slow recovery of cellular proliferation. Sphinxolides potently inhibited actin polymerization in vitro and the microfilament-dependent ATPase activity of purified actomyosin, indicating a direct effect on actin. Importantly, sphinxolides were equally cytotoxic toward MCF-7 human breast carcinoma cells and a subline which overexpresses P-glycoprotein (MCF-7/ADR). Similarly, overexpression of the **multidrug resistance** -associated protein MRP by HL-60 cells did not confer **resistance** to the sphinxolides. These studies demonstrate that sphinxolides are potent new antimicrofilament compounds that circumvent **multidrug resistance** mediated by overexpression of either P-glycoprotein or MRP. Therefore, these agents may be useful in the treatment of drug-**resistant** tumors.

1997

34/3,AB/13 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

03938814 Genuine Article#: QT664 Number of References: 63
Title: MDR EXPRESSION IN NORMAL-TISSUES - PHARMACOLOGICAL IMPLICATIONS FOR THE CLINICAL USE OF P-GLYCOPROTEIN INHIBITORS (Abstract Available)
Author(s): LUM BL; GOSLAND MP
Corporate Source: STANFORD UNIV,SCH MED,DIV ONCOL,CO BOX 37-1005,341 10TH ST/MONTARA//CA/94037; STANFORD UNIV,SCH MED/STANFORD//CA/94305; UNIV PACIFIC/STOCKTON//CA/95211; VET AFFAIRS MED CTR/PALO ALTO//CA/94304; UNIV KENTUCKY,COLL PHARM,LUCILLE P MARKEY CANC CTR/LEXINGTON//KY/00000
Journal: HEMATOLOGY-ONCOLOGY CLINICS OF NORTH AMERICA, 1995, V9, N2 (APR) , P319-336
ISSN: 0889-8588
Language: ENGLISH Document Type: ARTICLE
Abstract: In **multidrug resistance** , the MDR1 gene product, P-glycoprotein (P-gp) is thought to function as an efflux transport pump with broad specificity for a variety of anticancer drugs. The distribution of Pgp expression in normal human tissues with secretory function suggests P-gp may have a number of physiologic roles and that impeding P-gp function in these tissues with MDX modulators could result in increased **cytotoxin** concentrations and enhanced toxicity.

34/3,AB/16 (Item 1 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE

00796801 1998032746
SDZ PSC 833: A new MDR modulator
SDZ PCS 833: Un nuovo modulatore della MDR

Covelli A.
ADDRESS: A. Covelli, Clinical Research and Development, Lichstrasse 15, CH-4002 Basel, Switzerland
Journal: Tumori, 83/5 SUPPL. (S21-S24), 1997, Italy
PUBLICATION DATE: 19970000
CODEN: TUMOA
ISSN: 0300-8916
DOCUMENT TYPE: Conference Paper
LANGUAGES: Italian SUMMARY LANGUAGES: English
NO. OF REFERENCES: 24

SDZ PSC 833 is a novel compound able to reverse the **resistance** to chemotherapy of cancer cells with the **multidrug resistance** (MDR) phenotype by inhibiting the 170 kd P-glycoprotein (P-gp). In vitro studies show that SDZ PSC 833 directly interacts with, but is not transported by P-gp, although the exact mechanism of action has not yet been defined. In cells with the MDR phenotype, intracellular concentration of various P-gp-transported anticancer drugs is restored to the same level as in sensitive cells by SDZ PSC 833 concentrations of 0.8 muM to 3.0 muM. In vivo SDZ PSC 833 was highly active in potentiating the anti-tumour activity of all tested anticancer drugs (ACs) in both sensitive and MDR tumours. Sensitivity of non-MDR tumours was increased by SDZ PSC 833 through pharmacokinetic interactions, that result in enhanced area-under-the-curve (AUC) of P-gp-transported ACs. However, an increased AC bioavailability is not sufficient to explain the therapeutic benefit of SDZ PSC 833 co-treatment in MDR tumour-bearing mice: In these animals, no survival increase could be achieved with the AC alone by simply increasing the **cytotoxin** dosage up to doses that were severely toxic for the non-tumour-bearing mice. In a series of phase I/II studies, the recommended doses of SDZ PSC 833 were established at: 10 mg/kg/day iv as a 24-hour continuous infusion after a 2 mg/kg loading dose as a 2-hour infusion; 20 mg/kg orally divided four times daily in solid tumours or 16 mg/kg orally divided four times daily in multiple myeloma. The dose limiting toxicity of SDZ PSC 833 is ataxia, which appears to be reversible and dose-related. Moreover, a predictable change in pharmacokinetic parameters of concomitantly administered P-gp-transported AC(s) which usually necessitate a 30-60% reduction from the standard dose of the AC in order to maintain the same time-exposure and doserelated toxicity of the cytotoxic drug alone. The results of experiments both in vitro and in vivo suggested that adequate blood levels (ie <=1.0 muM) of SDZ PSC 833 must be reached before and maintained during the administration of concomitant AC(s), in order to maximally reverse MDR. At the recommended doses, blood concentrations exceeding 1000 ng/mL (1.0 muM) can be achieved after both iv and oral administration. Indeed, SDZ PSC 833 concentrations that fully reverse MDR in vitro are achievable in vivo: plasma samples from patients treated with SDZ PSC 833 restored the sensitivity of MDR human sarcoma cells to paclitaxel, etoposide and doxorubicin. Clinical studies completed so far aimed first to determine the dose of both SDZ PSC 833 and the concomitant AC(s) to be used in ongoing pivotal trials. These studies accrued advanced stage cancer patients, however, tumour responses have been observed in both solid and hematological tumours. The in vitro finding that treatment with SDZ PSC 833 may suppress the activation of the MDR1 gene and prevent the emergence of **resistant** cancer cell clones with the MDR phenotype might support the use of this MDR modulator in earlier stages of disease.

34/3,AB/18 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

06847117 EMBASE No: 1997129704
Kinetics of the multidrug transporter (P-glycoprotein) and its reversal
Stein W.D.

W.D. Stein, Department of Biological Chemistry, Silberman Institute of Life Sciences, Hebrew University, Jerusalem Israel
Physiological Reviews (PHYSIOL. REV.) (United States) 1997, 77/2 (545-590)
CODEN: PHREA ISSN: 0031-9333
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 260

Most cancer deaths result from the cancer's either being intrinsically **resistant** to chemotherapeutic drugs or becoming **resistant** after being initially sensitive. Often, in cells grown in cell culture, drug **resistance** correlates with the presence of one or more of the so-called P-glycoproteins or **multidrug resistance** proteins, products of the mdr family of genes. This review is largely concerned with the transport kinetics of the P- glycoproteins. We first present a brief overview of the P-glycoproteins, their properties, and their clinical significance. Later sections of the review expand on this material with special emphasis on the substrates of P- glycoprotein and how they cross the cell membrane, on the transport kinetics of the P-glycoprotein, on reversers of its action, and on its activity as an ATPase. In a final section, we consider the mechanism of action of P- glycoprotein as an actively transporting membrane pump. The characteristic of P-glycoprotein considered the most difficult to explain is its very broad specificity (or lack of specificity), but there are precedents for this property in well-known proteins such as serum albumin, which binds a range of molecular types, including substrates and reversers of P-glycoprotein, seemingly as broad as does P-glycoprotein. Pointing out this analogy does not provide a molecular explanation for the substrate-binding properties of P- glycoprotein but does make those properties more assimilable.

34/3,AB/20 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

06296599 EMBASE No: 1995321634
New compounds from cyanobacteria to circumvent MDR
Smith C.D.
Dept. of Pharmacology, Fox Chase Cancer Center, 7701 Burholme Avenue,Philadelphia, PA 19111 United States
Drug News and Perspectives (DRUG NEWS PERSPECT.) (Spain) 1995, 8/7 (423-425)
CODEN: DNPEE ISSN: 0214-0934
DOCUMENT TYPE: Journal; Short Survey
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Cyanobacteria have proven to be a rich source of new bioactive molecules, including several families of cytotoxins.

34/3,AB/22 (Item 1 from file: 94)
DIALOG(R)File 94:JICST-EPlus

00794027 JICST ACCESSION NUMBER: 89A0608658 FILE SEGMENT: JICST-E
Inhibition of multidrug- resistant **human tumor growth in athymic mice by anti-P-glycoprotein monoclonal antibodies.**
TSURUO T (1); HAMADA H (1); SATO S (1); HEIKE Y (1)
(1) Japanese Foundation for Cancer Research, Tokyo
Jpn J Cancer Res, 1989, VOL.80,NO.7, PAGE.627-631, FIG.2, REF.32
JOURNAL NUMBER: F0633ABW ISSN NO: 0910-5050
UNIVERSAL DECIMAL CLASSIFICATION: 615.277.3 615.37

LANGUAGE: English COUNTRY OF PUBLICATION: Japan
DOCUMENT TYPE: Journal
ARTICLE TYPE: Short Communication
MEDIA TYPE: Printed Publication
ABSTRACT: In an effort to devise an effective treatment for human drug-**resistant** cancers, we have developed monoclonal antibodies, MRK16 and 17, reactive to the **multidrug** transporter protein, P-glycoprotein. The monoclonal antibodies given intravenously effectively prevented tumor development in athymic mice inoculated subcutaneously with drug-**resistant** human ovarian cancer cells 2780AD. Treatment with MRK16 induced rapid regression of established subcutaneous tumors and apparent cures of some animals. Complement-dependent cytotoxicity (MRK16) and antibody-dependent cell-mediated cytolysis (MRK16 and 17) were observed with these antibodies. These monoclonal antibodies may have potential as treatment tools against **multidrug resistant** human tumors possessing the P-glycoprotein.(author abst.)

34/3,AB/26 (Item 1 from file: 266)
DIALOG(R)File 266:FEDRIP

00297884
IDENTIFYING NO.: 5R01CA52168-12 AGENCY CODE: CRISP
MODULATION OF MULTIDRUG RESISTANCE **MECHANISMS**
PRINCIPAL INVESTIGATOR: SIKIC, BRANIMIR I
ADDRESS: STANFORD UNIVERSITY SCH OF MED 269 CAMPUS DRIVE, CCSR-1105 STANFORD, CA 94305-5151
PERFORMING ORG.: STANFORD UNIVERSITY, STANFORD, CALIFORNIA
SPONSORING ORG.: NATIONAL CANCER INSTITUTE
FY : 2001
SUMMARY: The purpose of this proposal is to conduct clinical trials of modulation of resi stance to cytotoxic drugs. Studies of new modulators of MDR1/P-glycoprotein (P- gp) **multidrug resistance** (MDR) will continue. Additional areas of focus include : (1) modulation of other MDR mechanisms (the MDR-associated protein MRP, and th e bcl-2 family of inhibitors of apoptosis); and (2) the use of P-gp inhibitors t o enhance the oral bioavailability of taxanes and other P-gp substrate drugs. Ai m 1: To conduct Phase I trials of modulation of **multidrug resistance** mechanisms. We will conduct 1-2 Phase I trials per year, defining toxicities, optimal dose s and schedules, and drug disposition. Planned studies include: PSC 833 (PSC)/D oxil/paclitaxel; LY335979/mitoxantrone; LY335979/doxorubicin/paclitaxel; and oth er, new MDR1 modulators. Similar approaches will be applied to a new inhibitor o f MRP, with doxorubicin and with etoposide; and antisense oligonucleotide drugs against bcl-2 and bcl-xl. We will choose these new agents based on animal toxic ology, other preclinical data, and availability for clinical trials. An eventua l goal is combined blockade of two mechanisms (e.g., MDR1 and MRP). Aim 2: To st udy pharmacokinetic interactions associated with modulation of drug **resistance** . An important issue with modulators of drug **resistance** is the effect of these dr ugs on normal tissue function and in particular on the disposition of cytotoxins . Pharmacokinetic studies will involve compartmental methods to further define d rug interactions, and validation of optimal sampling strategies with Bayesian es timations. The effect of different modulators (PSC vs. LY335979) on the erythro mycin breath test in patients will be used to dissect the role of cytochrome P45 0 3A4 in these interactions. Ancillary pharmacokinetic studies of mitoxantrone and etoposide for the ECOG and POG trials of MDR1 modulation in acute myeloid le ukemias will also be supported. Aim 3: To enhance the oral bioavailability of MD R1-related drugs by co-administration with inhibitors of P-gp. Intestinal P-gp is a major barrier to the absorption of taxanes and other MDR1 related **cytotoxin** s. We will co-administer modulators and cytotoxins in trials designed to enhanc e bioavailability, and potentially

to increase the safety and convenience of che motherapy. Patients will receive an initial course of the **cytotoxin** intravenous ly, followed by sequential courses of the **cytotoxin** orally together with increas ing doses of the P-gp inhibitor. The first protocol in this aim will involve pa clitaxel with PSC. Other cytotoxins of interest for this approach include taxot ere, etoposide, and vinorelbine.

34/3,AB/27 (Item 2 from file: 266)
DIALOG(R)File 266:FEDRIP

00296058
IDENTIFYING NO.: 5R01CA12623-28 AGENCY CODE: CRISP
ANTITUMOR AGENTS FROM BLUE-GREEN ALGAE
PRINCIPAL INVESTIGATOR: MOORE, RICHARD E
ADDRESS: UNIVERSITY OF HAWAII 2545 THE MALL HONOLULU, HI 96822
PERFORMING ORG.: UNIVERSITY OF HAWAII AT MANOA, HONOLULU, HAWAII
SPONSORING ORG.: NATIONAL CANCER INSTITUTE
FY : 2001
SUMMARY: The long term goal of this research is to discover new antitumor drugs from blue-green algae (cyanobacteria). The research will be concerned primarily with searching for and finding cytotoxins that are significantly active against slow-growing solid tumors which account for most of the cancer deaths in the United States. Not only will it be important to discover new agents that are effective against solid tumors, but one which are capable of overcoming two major problems that develop in cancer patients undergoing chemotherapy, viz. multiple-drug- resistance (MDR) and myelosuppression. Two types of anti-MDR drugs are needed: (1) ones that are equally efficacious toward drug-sensitive and drug-resistant tumors and (2) ones that are able to potentiate the cytotoxicity of standard antitumor drugs like vinblastine and adriamycin toward drug-resistant cells, i.e. reverse MDR. Using disk diffusion assays to screen a large number of extracts of cultured blue-green algae for selective cytotoxicity, it has been found that 0.8 percent of the extracts are solid tumor selective, i.e. more cytotoxic toward murine and/or human solid tumor cells that leukemia cells, and that an additional 0.8 percent of the extracts are tumor selective, i.e. more cytotoxic toward tumor (e.g. leukemia) cells than normal cells such as CFU-GM, the stem cell of murine hematopoietic tissue. Several solid tumor selective and tumor selective cytotoxins have already been isolated and identified from these extracts, but relatively few of them have been evaluated in vivo. The first task of this project in the in vivo evaluation of several natural and semi-synthetic analogs of tantazoles, mirabazoles, scytophycins and mirabimide E from Scytonema mirabile BY-8-1 and S. pseudohormanni BC-1-2 and aulosirazole from Aulosira fertillissima DO-8-1. The next task is the isolation, structure determination, and pharmacological evaluation of the solid tumor selective cytotoxins in Calothrix gloeocola DT-21-1, Hapalosiphon hibernicus DU-56-1, Tolypothrix scytonematoides HZ-48-1, Scytonema hofmanni HZ-50-1, T. byssoidea IA-5-1, Plectonema radiosum IA-82-2, Scytonema fremyii IA-90-1, and Stigonema sp. II-1 and the tumor selective cytotoxins in Oscillatoria foreaui ATCC 27935, Lyngbya lagerheimii ATCC 29125, Ctenocladus cincinnatus BN-11-1, Nostoc sp. BR-8-2, Phormidium tenue CB-1-1, Calothrix viguieri CCAP 1410/6, Plectonema hansgirgi CN-2-2, Plectonema radiosum DT-65-1, Phormidium rubroterricola DV-8-1, Phormidium bohneri IC-58-1, Nostoc sp. IE-87-1 and IE-87-3, and Porphyrosiphon notarisii UTEX 1816. The next tasks are the isolation, identification and pharmacological evaluation of the taxol-like cytotoxins in five cyanophytes, the non-selective cytotoxins in nine more cyanophytes, and the MDR-reversing agents in still another 17 blue-greens. The last tasks are the isolation, identification and evaluation of the potent **cytotoxin** in Aulosira fertillisima DU-18-1 and the potent fungicidal cytotoxins in five cyanophytes.

34/3,AB/29 (Item 1 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

00395138
RECEPTOR AND TRANSPORTER ANTAGONISTS
ANTAGONISTES RECEPTEURS ET TRANSPORTEURS
Patent Applicant/Assignee:
NG Gordon Y K,
SEEMAN Philip,
GEORGE Susan R,
O'DOWD Brian F,
Inventor(s):
NG Gordon Y K,
SEEMAN Philip,
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O'DOWD Brian F,
Patent and Priority Information (Country, Number, Date):
Patent: WO 9735881 A2 19971002
Application: WO 97CA203 19970326 (PCT/WO CA9700203)
Priority Application: US 9614306 19960327; US 96670119 19960625; US 9624240 19960820
Designated States: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN GH KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
Publication Language: English
Fulltext Word Count: 24703

English Abstract
Specific antagonists for prokaryotic or eukaryotic integral membrane proteins are provided. The antagonists are peptides having the amino acid sequence of a transmembrane domain of the integral membrane proteins or of a portion of analogue thereof. Methods are provided for preventing or treating disorders characterised by disordered function of an integral membrane protein by administration of a specific peptide antagonist of the integral membrane protein.

French Abstract
La presente invention concerne des antagonistes specifiques de proteines intrinseques procaryotes et eucaryotes. Lesdits antagonistes sont des peptides presentant la sequence d'acides amines d'un domaine membranaire desdites proteines intrinseques ou d'une portion ou d'un analogue de ces dernieres. On decrit egalement des procedes permettant de prevenir ou de traiter des troubles caracterises par des troubles fonctionnels d'une proteine intrinseque en administrant un peptide antagoniste specifique de la proteine intrinseque.
?

34/3,AB/16 (Item 1 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE

00796801 1998032746
SDZ PSC 833: A new MDR modulator
SDZ PCS 833: Un nuovo modulatore della MDR
Covelli A.
ADDRESS: A. Covelli, Clinical Research and Development, Lichstrasse 15, CH-4002 Basel, Switzerland
Journal: Tumori, 83/5 SUPPL. (S21-S24), 1997, Italy
PUBLICATION DATE: 19970000
CODEN: TUMOA
ISSN: 0300-8916
DOCUMENT TYPE: Conference Paper
LANGUAGES: Italian SUMMARY LANGUAGES: English
NO. OF REFERENCES: 24

SDZ PSC 833 is a novel compound able to reverse the **resistance** to chemotherapy of cancer cells with the **multidrug resistance** (MDR) phenotype by inhibiting the 170 kd P-glycoprotein (P-gp). In vitro studies show that SDZ PSC 833 directly interacts with, but is not transported by P-gp, although the exact mechanism of action has not yet been defined. In cells with the MDR phenotype, intracellular concentration of various P-gp-transported anticancer drugs is restored to the same level as in sensitive cells by SDZ PSC 833 concentrations of 0.8 muM to 3.0 muM. In vivo SDZ PSC 833 was highly active in potentiating the anti-tumour activity of all tested anticancer drugs (ACs) in both sensitive and MDR tumours. Sensitivity of non-MDR tumours was increased by SDZ PSC 833 through pharmacokinetic interactions, that result in enhanced area-under-the-curve (AUC) of P-gp-transported ACs. However, an increased AC bioavailability is not sufficient to explain the therapeutic benefit of SDZ PSC 833 co-treatment in MDR tumour-bearing mice: In these animals, no survival increase could be achieved with the AC alone by simply increasing the **cytotoxin** dosage up to doses that were severely toxic for the non-tumour-bearing mice. In a series of phase I/II studies, the recommended doses of SDZ PSC 833 were established at: 10 mg/kg/day iv as a 24-hour continuous infusion after a 2 mg/kg loading dose as a 2-hour infusion; 20 mg/kg orally divided four times daily in solid tumours or 16 mg/kg orally divided four times daily in multiple myeloma. The dose limiting toxicity of SDZ PSC 833 is ataxia, which appears to be reversible and dose-related. Moreover, a predictable change in pharmacokinetic parameters of concomitantly administered P-gp-transported AC(s) which usually necessitate a 30-60% reduction from the standard dose of the AC in order to maintain the same time-exposure and doserelated toxicity of the cytotoxic drug alone. The results of experiments both in vitro and in vivo suggested that adequate blood levels (ie <=1.0 muM) of SDZ PSC 833 must be reached before and maintained during the administration of concomitant AC(s), in order to maximally reverse MDR. At the recommended doses, blood concentrations exceeding 1000 ng/mL (1.0 muM) can be achieved after both iv and oral administration. Indeed, SDZ PSC 833 concentrations that fully reverse MDR in vitro are achievable in vivo: plasma samples from patients treated with SDZ PSC 833 restored the sensitivity of MDR human sarcoma cells to paclitaxel, etoposide and doxorubicin. Clinical studies completed so far aimed first to determine the dose of both SDZ PSC 833 and the concomitant AC(s) to be used in ongoing pivotal trials. These studies accrued advanced stage cancer patients, however, tumour responses have been observed in both solid and hematological tumours. The in vitro finding that treatment with SDZ PSC 833 may suppress the activation of the MDR1 gene and prevent the emergence of **resistant** cancer cell clones with the MDR phenotype might support the use of this MDR modulator in earlier stages of disease.

39/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08882388 96163326 PMID: 8562335
Regulation of P - glycoprotein 1 and 2 gene expression and protein activity in two MCF- 7/Dox cell line subclones.
Davies R; Budworth J; Riley J; Snowden R; Gescher A; Gant TW
MRC Toxicology Unit, Leicester, UK.
British journal of cancer (SCOTLAND) Feb 1996, 73 (3) p307-15, ISSN 0007-0920 Journal Code: AV4
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The **MCF - 7** doxorubicin-**resistant** cell line **MCF -7** /Dox has been used extensively for studies of the **multidrug resistance** phenomenon. Using fluorescence-activated cell sorting (FACS), these cells were separated into two populations on the basis of rhodamine 123 (R123) accumulation. We designated these as low **P -glycoprotein** (LP-gp) and high P-gp (HP-gp) cells on the basis of their P-gp content. Using the reverse transcriptase polymerase chain reaction technique controlled by homologous internal standards, we analysed levels of MDR1 and MDR2 mRNA in each cell type. LP-gp and HP-gp cells had MDR1 mRNA levels of 2.17 +/- 0.17 and 6.65 +/- 2.29 amol ng-1 total RNA respectively, compared with 0.00088 +/- 0.00005 amol ng-1 in wild-type **MCF -7** cells (**MCF -7** /WT). **MCF -7** /WT cells additionally contained 0.023 +/- 0.016 amol ng-1 of MDR2 mRNA, which was unchanged in LP-gp cells, but lower than in HP-gp cells, which contained 0.42 +/- 0.08 amol ng-1. Both LP-gp and HP-gp cells contained increased copies of the MDR1 gene. However, the degree of gene amplification did not correlate with the changes in MDR1 mRNA levels, indicating further regulatory levels of gene expression. The level of P-gp detected by MRK 16 correlated with R123 accumulation. HP-gp cells expressed a 10-fold higher level of P-gp1 than LP-gp cells. However, there was only a 3-fold increase in MDR1 mRNA level in HP-gp cells compared with LP-gp cells. These data suggest that some regulation of P-gp1 expression also occurred at the post-translational level. Phosphorylation of P-gp by protein kinase C (PKC)-alpha is necessary for its activity. Our analysis of PKC-alpha, 0 and epsilon isozyme levels, and subcellular distribution, shows a co-regulation of expression with P-gp, suggesting a necessary role for PKC in P-gp regulation.

39/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08648208 96064752 PMID: 7592889
Partial inhibition of multidrug resistance by safingol is independent of modulation of P - glycoprotein substrate activities and correlated with inhibition of protein kinase C.
Sachs CW; Safa AR; Harrison SD; Fine RL
Division of Hematology-Oncology, Duke University Medical Center, Durham, North Carolina 27705, USA.
Journal of biological chemistry (UNITED STATES) Nov 3 1995, 270 (44) p26639-48, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: CA-56078, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Safingol is a lysosphingolipid protein kinase C (PKC) inhibitor that competitively interacts at the regulatory phorbol binding domain of PKC. We investigated the effects of safingol on antineoplastic drug sensitivity and PKC activity of **MCF - 7** tumor cell lines. Safingol treatment of 32P-labeled **MCF -7** WT and **MCF -7** DOXR cells inhibited phosphorylation of the myristoylated alanine-rich protein kinase C substrate in both cell

lines, suggesting inhibition of cellular PKC. However, only in **MCF** -7 DOXR cells did safingol treatment increase accumulation of [3H]vinblastine and enhance toxicity of Vinca alkaloids and anthracyclines. Drug accumulation changes in **MCF** -7 DOXR cells treated with safingol were accompanied by inhibition of basal and phorbol 12,13-dibutyrate-stimulated phosphorylation of **P -glycoprotein** (P-gp). Expression of P-gp and levels of mdr1 message in **MCF** - 7 DOXR cells were not altered by safingol treatment alone or in combination with vinblastine. Treatment of **MCF** -7 DOXR cell membranes with safingol did not inhibit [3H]vinblastine binding or [3H]azidopine photoaffinity labeling of P-gp. Furthermore, safingol did not stimulate P-gp ATPase activity in membranes prepared from **MCF** -7 DOXR cells. We conclude that enhanced drug accumulation and sensitivity in **MCF** -7 DOXR cells treated with safingol are correlated with inhibition of PKC rather than competitive interference with P-gp drug binding through direct interaction with **P glycoprotein** .

39/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08300084 95080858 PMID: 7989120
P - glycoprotein **expression in the Golgi apparatus of** multidrug-resistant **cells.**
Molinari A; Cianfriglia M; Meschini S; Calcabrini A; Arancia G
Laboratorio di Ultrastrutture, Istituto Superiore di Sanita, Rome, Italy.
International journal of cancer. Journal international du cancer (UNITED STATES) Dec 15 1994, 59 (6) p789-95, ISSN 0020-7136 Journal Code: GQU
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The surface and intracellular expression of mdrI-**P -glycoprotein** in parental drug-sensitive human breast cancer cells (**MCF** -7) and their **multidrug - resistant** (MDR) variants has been studied by using the monoclonal antibodies (MAbs) MM4.17 and MRK-16, which recognize 2 different epitopes of the drug efflux pump molecule. Fluorescence microscopic observations showed that **P -glycoprotein** , in addition to being located at the cell surface, can also be found in the Golgi apparatus of **resistant** cells. To confirm this finding, Golgi apparatus and **P -glycoprotein** were double-labelled with wheat-germ agglutinin (WGA) and MAb MM4.17. Laser scanning confocal microscopy indicated that, in MDR cells, Adriamycin mainly accumulated cytoplasmically in a perinuclear region. This accumulation proved to be modulated by pre-treatment with verapamil or ATP depletion. Moreover, the vital staining of Adriamycin-treated MDR cells, performed with the fluorescent lipid N-[7-(4-nitrobenzo-2-oxa-1,3-diazole)] - 6-aminocaproyl sphingosine (C6-NBD-ceramide), revealed that the anthracyclinic antibiotic was located in the Golgi apparatus. All these results indicate that the drug transporter is located in the Golgi apparatus, in which Adriamycin molecules also accumulate.

39/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08250098 95007968 PMID: 7923555
Quercetin potentiates the effect of adriamycin in a multidrug-resistant MCF- 7 **human breast-cancer cell line:** P- glycoprotein **as a possible target.**
Scambia G; Ranelletti FO; Panici PB; De Vincenzo R; Bonanno G; Ferrandina G; Piantelli M; Bussa S; Rumi C; Cianfriglia M; et al
Department of Gynecology, Catholic University, Rome, Italy.
Cancer chemotherapy and pharmacology (GERMANY) 1994, 34 (6) p459-64, ISSN 0344-5704 Journal Code: C9S

Comment in Cancer Chemother Pharmacol. 1995;36(5) 448-50
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

This study demonstrates that the flavonoid quercetin (Q), a plant-derived compound with low toxicity in vivo, greatly potentiates the growth-inhibitory activity of Adriamycin (ADR) on **MCF -7** ADR-**resistant** human breast cancer cells. The effect of Q was dose-dependent at concentrations ranging between 1 and 10 microM. Since ADR **resistance** in these cells is associated with the expression of high levels of **P - glycoprotein** (Pgp), we evaluated the effect of Q and related flavonoids of Pgp activity in cytofluorographic efflux experiments with the fluorescent dye rhodamine 123 (Rh 123). Our results indicate that Q and 3-OMe Q (3',4',7-trimethoxyquercetin) but not the 3-rhamnosylglucoside of Q (rutin) inhibit the Pgp pump-efflux activity in a dose-related manner. Moreover, 10 microM Q reduces the expression of the immunoreactive Pgp in **MCF -7** ADR-**resistant** cells as evaluated by cytofluorimetric assay. In conclusion, these findings provide a further biological basis for the potential therapeutic application of Q as an anti-cancer drug either alone or in combination with ADR in **multidrug resistant** breast tumor cells.

39/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07016732 93059423 PMID: 1359153

Effect of P - glycoprotein **expression on sensitivity to hormones in** MCF- 7 **human breast cancer cells.**

Clarke R; Currier S; Kaplan O; Lovelace E; Boulay V; Gottesman MM; Dickson RB

Vincent T. Lombardi Cancer Research Center, Georgetown University Medical School, Washington, D.C. 20007.

Journal of the National Cancer Institute (UNITED STATES) Oct 7 1992, 84 (19) p1506-12, ISSN 0027-8874 Journal Code: J9J
Contract/Grant No.: UO1CA-51908, CA, NCI
Comment in J Natl Cancer Inst. 1992 Oct 7;84(19) 1458-60
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

BACKGROUND: Data obtained from studies of primary human breast cancers and established cell lines indicate that overexpression of the MDR1 gene (also known as PGY1) is associated with decreased expression of steroid hormone receptors and increased expression of epidermal growth factor (EGF) receptors. Other study results indicate that both progestins and triphenylethylene antiestrogens may be substrates for **P -glycoprotein** , the product of the MDR1 gene. These findings together suggest an association between overexpression of the MDR1 gene and cross-**resistance** to progestin and antiestrogen therapies. PURPOSE: This study was designed to determine (a) the ability of MDR1 expression to alter tumor sensitivity to hormone therapy and (b) the role of MDR1 expression in expression of functional hormone receptors in human breast cancer. METHODS: We transduced **MCF - 7** cells with MDR1 complementary DNA, using a retroviral vector directing the constitutive expression of the MDR1 gene. Transduced cells (MCF-7MDR1) were examined for ability to produce **P -glycoprotein** , expression of steroid hormone receptors, and responsivity to antiestrogens. For comparison, we used MCF-7ADR human breast cancer cells, which overexpress MDR1 and have also lost the requirement for 17 beta-estradiol supplementation to form tumors in nude mice. We also investigated the level of EGF-R mRNA expression by using a sensitive RNase protection analysis. RESULTS: MCF-7MDR1 cells retained both estrogen receptor and progesterone receptor expression as well as sensitivity to 4-hydroxytamoxifen. Expression of the estrogen-inducible pS2 and EGF receptor genes was similar in parental **MCF - 7** and transduced MCF-7MDR1 cells. EGF receptor

expression was increased, and pS2 expression was lost (undetectable) in MCF-7ADR cells. CONCLUSIONS: The data indicate that overexpression of the MDR1 gene alone confers a **multidrug -resistant** phenotype, but it does not directly result in either cross-**resistance** to antiestrogens or a loss of steroid hormone receptor expression. IMPLICATIONS: MCF-7MDR1 cells provide an important model for study of the interactions of cytotoxic drugs, hormones, and the MDR1 glycoprotein in human hormone-responsive breast cancer cells.

39/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06930727 93046198 PMID: 1358437
A new functional role for P - glycoprotein : efflux pump for benzo(alpha)pyrene in human breast cancer MCF- 7 cells.
Yeh GC; Lopaczynska J; Poore CM; Phang JM
Laboratory of Nutritional and Molecular Regulation, National Cancer Institute, NIH, Frederick, Maryland 21702.
Cancer research (UNITED STATES) Dec 1 1992, 52 (23) p6692-5, ISSN 0008-5472 Journal Code: CNF
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We propose that the cellular burden of certain carcinogens may be mitigated by **P -glycoprotein** (P-gp), the putative drug efflux pump. In a series of **multidrug resistant** human breast cancer **MCF -7** cells with increasing P-gp expression we examined this hypothesis using benzo(alpha)pyrene, a widely distributed environmental and dietary carcinogen. We found that **multidrug resistant** cells were cross- **resistant** to benzo(alpha)pyrene and the rates of efflux for benzo(alpha)pyrene were higher in **multidrug resistant** cells than in wild type cells. Evidence supporting the involvement of P-gp included the inhibition of azidopine binding to P-gp benzo(alpha)pyrene and the inhibition of benzo(alpha)pyrene efflux by Adriamycin and verapamil. Our findings suggest that P-gp may play a role in the cellular defense to carcinogens. The expression of P-gp and the modulation of its function may affect the susceptibility of normal tissues to transformation by carcinogens.

39/3,AB/32 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10679804 BIOSIS NO.: 199799300949
P- glycoprotein location and drug distribution in sensitive and resistant cells.
AUTHOR: Arancia G(a); Cianfriglia M; Molinari A(a); Calcabrini A(a); Meschini S(a)
AUTHOR ADDRESS: (a)Lab. Ultrastutture, Ist. Superiore Sanita, Rome**Italy
JOURNAL: Cytotechnology 19 (3):p257 1996
CONFERENCE/MEETING: ETCS (European Tissue Culture Society) Meeting on Drug Resistance in Cancer Dublin, Ireland September 20-23, 1995
ISSN: 0920-9069
RECORD TYPE: Citation
LANGUAGE: English
1996

39/3,AB/33 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10581788 BIOSIS NO.: 199699202933
Reversal of P- glycoprotein-**mediated** multidrug resistance **by a potent cyclopropyldibenzosuberane modulator, LY335979.**
AUTHOR: Dantzig Anne H(a); Shepard Robert L; Cao Jin; Law Kevin L; Ehlhardt William J; Baughman Todd M; Bumol Thomas F; Starling James J
AUTHOR ADDRESS: (a)Lilly Res. Lab., Lilly Corporate Cent., Eli Lilly and Co., Indianapolis, IN 46285-0424**USA
JOURNAL: Cancer Research 56 (18):p4171-4179 1996
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Overexpression of **P -glycoprotein** (Pgp) by tumors results in **multidrug resistance** (MDR) to structurally unrelated oncolytics. MDR cells may be sensitized to these oncolytics when treated with a Pgp modulator. The present study evaluates LY335979 as a modulator both in vitro and in vivo. LY335979 (0.1 mu-M) fully restored sensitivity to vinblastine, doxorubicin (Dox), etoposide, and Taxol in CEM/VLB-100 cells. LY335979 modulated Dox cytotoxicity even when LY335979 (0.5 mu-M) was removed 24 h prior to the cytotoxicity assay. LY335979 blocked (3H)azidopine photoaffinity labeling of the M-r apprx 170,000 Pgp in CEM/VLB-100 plasma membranes and competitively inhibited equilibrium binding of (3H)vinblastine to Pgp (K-i of apprx 0.06 mu-M). Treatment of mice bearing P388/ADR murine leukemia cells with LY335979 in combination with Dox or etoposide gave a significant increase in life span with no apparent alteration of pharmacokinetics. LY335979 also enhanced the antitumor activity of Taxol in a MDR human non-small cell lung carcinoma nude mouse xenograft model. Thus, LY335979 is an extremely potent, efficacious modulator that apparently lacks pharmacokinetic interactions with coadministered anticancer drugs and is, therefore, an exciting new agent for clinical evaluation for reversal of Pgp-associated MDR.

1996

39/3,AB/44 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09443559 BIOSIS NO.: 199497451929
Reversal of P- glycoprotein-**mediated** multidrug resistance **by pure anti-oestrogens and novel tamoxifen derivatives.**
AUTHOR: Kirk Julie(a); Syed Samiuddin K; Harris Adrian L; Jarman Michael; Roufogalis Basil D; Stratford Ian J; Carmichael Jaems
AUTHOR ADDRESS: (a)Univ. Lab. Physiol., Oxford OX1 3PT**UK
JOURNAL: Biochemical Pharmacology 48 (2):p277-285 1994
ISSN: 0006-2952
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In this study the ability of five novel anti-oestrogens (4-iodotamoxifen, pyrrolidino-4-iodotamoxifen, ethyl bromide tamoxifen (EBTx), ICI 164,384 (ICI 164) and ICI 182,7801 to alter drug toxicity to **multidrug resistant** cell lines have been compared. The effect of these compounds on ATP-dependent vinblastine (VBL) transport was also tested using inside-out vesicles (IOV) prepared from highly **P -glycoprotein** (Pgp)-expressing CCRF-CEM/VBL-1000 cells. The pure anti-oestrogen ICI 164 was most effective, enhancing doxorubicin and VBL toxicity to **MCF -7** -Adr cells 25- and 35-fold, respectively, and was also the best inhibitor of ATP-dependent (3H)VBL accumulation by IOV. Pure anti-oestrogens,

tamoxifen and iodotamoxifens completely reversed VBL **resistance** in the mdr1 transfected lung cancer cell line, S1/1.1, where **resistance** relative to wild-type cells was mediated solely by Pgp. The membrane impermeant tamoxifen derivative EBTX did not modify drug **resistance** , yet was as effective an inhibitor of VBL accumulation by inside-out Pgp-positive vesicles as tamoxifen. This indicates an intracellular role for tamoxifen and its derivatives in the modulation of Pgp-mediated drug **resistance** .

1994

39/3,AB/48 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08484837 BIOSIS NO.: 199344034837
Modulation of P- glycoprotein **mediated** multidrug resistance **by verapamil analogs.**
AUTHOR: Vaidyanathan S(a); Bhardwaj R(a); Engineer F N; Desai P B(a)
AUTHOR ADDRESS: (a)Sch. Pharm., Northeast Louisiana Univ., Monroe, La. 71209
JOURNAL: Pharmaceutical Research (New York) 9 (10 SUPPL.):pS348 1992
CONFERENCE/MEETING: American Association of Pharmaceutical Scientists 1992 Annual Meeting and Exposition San Antonio, Texas, USA November 15-19, 1992
ISSN: 0724-8741
RECORD TYPE: Citation
LANGUAGE: English
1992

39/3,AB/75 (Item 1 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

02511971
Utility
HYBRIDOMA PRODUCING MONOCLONAL ANTIBODY F4 WHICH SPECIFICALLY BINDS TO **MULTIDRUG RESISTANT P -GLYCOPROTEIN** AND ASSAYS FOR DETECTION OF **P - GLYCOPROTEIN**
[For detection of drug-resistant cancer cells without biopsy]

PATENT NO.: 5,503,984
ISSUED: April 02, 1996 (19960402)
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[Assignee Code(s): 11684]
EXTRA INFO: Assignment transaction [Reassigned], recorded April 15, 1996 (19960415)
Assignment transaction [Reassigned], recorded May 4, 1998 (19980504)
Assignment transaction [Reassigned], recorded June 2, 1998 (19980602)
APPL. NO.: 8-47,117
FILED: April 13, 1993 (19930413)

FULL TEXT: 895 lines

ABSTRACT

A unique monoclonal antibody against **P -glycoprotein** . The monoclonal antibody is different than those previously described and has the surprising property of reacting to a soluble form of **P -glycoprotein** . The invention further includes a novel hybridoma cell line which produces the antibody. A preferred embodiment of the novel antibody has been designated F4 which is believed to react at or near an extracellular transmembrane loop of **P -glycoprotein** selected from the group consisting of the third and sixth extracellular loops. The invention further comprises a method for detecting the presence of **P -glycoprotein** comprising reacting a specimen containing **P -glycoprotein** with the novel monoclonal antibody and detecting the reaction to show that **P -glycoprotein** is present. The invention, in a preferred embodiment, comprises detecting the presence of drug resistant carcinoma cells, in the absence of biopsy, comprising removing extracellular fluids from a patient for use as a specimen, and determining the presence of **P - glycoprotein** in the specimen by reacting the specimen with the the novel monoclonal antibody to show that **P -glycoprotein** is present as an indicator of drug resistance. The extracellular fluid may be any suitable fluid which could contain **P - glycoprotein** as an indicator of drug resistance. Such fluids may for example be plasma, lymph excretions, and especially ascites taken from the area of a tumor site.
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